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(71) Applicant: GEORGIA TECH RESEARCH CORPORATION [US/US]; 400 Tenth Street, Centennial Research Building, Atlanta, GA 30332-0414 (US).

(72) Inventors: PRAUSNITZ, Mark, R.; 417 West Howard Avenue, Decatur, GA 30030 (US). ALLEN, Mark, G.; 425 Spalding Drive, Atlanta, GA 30328 (US). HENRY, Sebastien; 1511 Vinings Parkway, Smyrna, GA 30080 (US). MCALLISTER, Devin, V.; 49 Geddes Street, Holley, NY 14470 (US). ACKLEY, Donald, E.; 2033 Cambridge Avenue, Cardiff, CA 92007 (US). GUJRAL, Inder-Jeet; 111-9 Trowbridge Street, Cambridge, MA 02138 (US). JACKSON, Thomas; 7135 Olivetas Avenue, La Jolla, CA 92037 (US).

(74) Agents: PABST, Patrea, L. et al.; Arnall Golden & Gregory, LLP, 2800 One Atlantic Center, 1201 West Peachtree Street, Atlanta, GA 30309-3450 (US).

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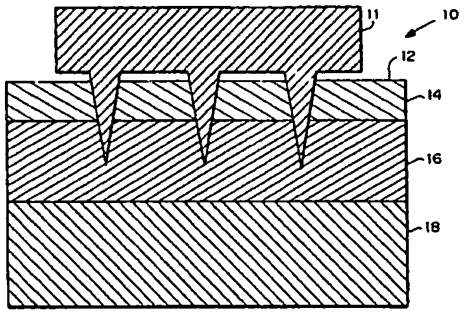
(54) Title: DEVICES AND METHODS FOR ENHANCED MICRONEEDLE PENETRATION OF BIOLOGICAL BARRIERS



(57) Abstract: Microneedle devices are provided for delivery of drugs across biological tissue and for controlled sampling of biological fluids in a minimally-invasive, painless, and convenient manner. The devices permit 1) drug delivery at clinically relevant rates across or into skin or other tissue barriers, and/or 2) *in vivo* sensing or withdrawal of biological fluids from the body, particularly from or through the skin or other tissue barriers. Drug delivery devices preferably include a plurality of hollow microneedles attached to or integrated into a substrate, and at least one reservoir (containing drug) selectably in communication with the microneedles, wherein the amount of drug to be delivered can be selectively altered. Withdrawal or sensing microneedle devices preferably include microneedles attached to or integrated into a substrate, and at least one collection chamber and or sensor in communication with the microneedles. Preferred embodiments further include a means for inducing biological fluid, such as interstitial fluid, to be drawn through the microneedles and into the collection chamber for analysis. Also provided are microneedle devices and methods for the enhanced transport of molecules across tissue by improving the interaction of an array of microneedles and a deformable, elastic biological barrier, such as human skin. The devices and methods act to 1) limit the elasticity, 2) adapt to the elasticity, 3) utilize alternate ways of creating the holes for the microneedles to penetrate the biological barrier, other than the simply direct pressure of the microneedle substrate to the barrier surface, or 4) combination of 1)-3).

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We claim:

1. A device for transport of a material across or into a biological barrier comprising

a) a plurality of hollow microneedles each having a base end and a tip, with at least one hollow pathway disposed at or between the base end and the tip,

b) a substrate to which the base ends of the microneedles are attached or integrated, and

c) at least one reservoir which is in connection with the base ends of at least one of the microneedles, either integrally or separably until the moment of use,

wherein the volume or amount of material to be transported can selectively be altered.

2. The device of claim 1 wherein the reservoir is formed of a material which is deformable.

3. The device of claim 2 wherein the reservoir is elastic.

4. The device of claim 1 wherein the reservoir further comprises a therapeutic, prophylactic, or diagnostic agent.

5. The device of claim 4 wherein the agent is selected from the group consisting of peptides, proteins, carbohydrates, nucleic acid molecules, lipids, organic molecules, biologically active inorganic molecules, and combinations thereof.

6. The device of claim 1 further comprising a plunger movably secured to the substrate, wherein the plunger can compress the reservoir.

7. The device of claim 6 further comprising a spring engaged with the plunger.

8. The device of claim 1 wherein the diameter of the microneedles is between about 10 μm and about 200 μm.

9. The device of claim 1 wherein the length of the microneedles is between about 100 μm and 1 mm.

10. The device of claim 1 wherein the microneedles are adapted to provide an insertion depth of less than about 100 to 150 μm.

11. The device of claim 1 comprising a three dimensional array of microneedles.

12. The device of claim 1 further comprising an adhesive material for

securing the device during delivery.

13. The device of claim 1 wherein the reservoir is a syringe or pump connected to the substrate.

14. The device of claim 1 comprising an attachment means for securing the device to a syringe or pump.

15. The device of claim 13 wherein the substrate is adapted to removably connect to a standard or Luer-lock syringe.

16. The device of claim 1 further comprising a sealing mechanism which is interposed between the reservoir and the substrate or which is secured to the tips of the microneedles.

17. The device of claim 16 wherein the sealing mechanism is a fracturable barrier interposed between the reservoir and the substrate.

18. The device of claim 1 further comprising a means for providing feedback to indicate that delivery has been initiated or completed.

19. The device of claim 1 wherein at least the microneedles are manufactured for single use as a disposable reagent.

20. The device of claim 1 wherein the device further comprises means for stopping delivery.

21. The device of claim 1 further comprising an osmotic pump to move agent.

22. The device of claim 1 wherein the microneedle is at an angle other than perpendicular to the substrate.

23. The device of claim 1 wherein the substrate is formed of a flexible material.

24. The device of claim 1 comprising multiple compartments or reservoirs.

25. The device of claim 24 wherein the compartments or reservoirs can be connected or in communication with each other.

26. The device of claim 24 wherein one or more reservoirs contain a solid formulation and one or more reservoirs contains a liquid carrier for the solid formulation.

27. The device of claim 1 in a packaging that protects the device from damage and/or contamination.

28. The device of claim 1 further comprising a removable liner that covers

the microneedle tips and that can be used to protect and/or seal access to or from the microneedles.

29. The device of claim 1 wherein the device comprises rate control means, which can be used to regulate the rate or extent at which materials flow through the microneedles.

30. The device of claim 29 wherein the rate control means is a membrane at one end of the microneedles through which agent or fluid must pass.

31. The device of claim 29 wherein the rate control means is a material positioned within the hollow pathway of the microneedles.

32. The device of claim 1 comprising multiple microneedle arrays in combination with means for accessing one or more arrays at a time.

33. The device of claim 1 comprising means for preventing undesired contact with or use of the microneedles.

34. The device of claim 33 wherein the means is packaging that covers the microneedles.

35. The device of claim 33 wherein the means is packaging that shears off the microneedles, or tips thereof, after use.

36. The device of claim 33 wherein the means are materials which are delivered into the hollow pathways to seal the microneedles.

37. A method for delivering a therapeutic, prophylactic or diagnostic agent across or into tissue comprising

inserting into the tissue one or more microneedles that are in fluid connection with at least one reservoir containing the agent to be delivered, and

reducing the volume or amount of the agent in the reservoir by driving the agent through at least one of the microneedles.

38. The method of claim 37 wherein the reservoir is formed of a material which is deformable.

39. The method of claim 37 wherein the volume or amount of the agent in the reservoir is reduced by depressing a plunger that is movably secured to the substrate.

40. A kit of parts for delivering a therapeutic, prophylactic or diagnostic agent across or into tissue comprising

(a) one or more microneedle devices which comprise a plurality of hollow

microneedles. a substrate to the microneedles are attached or integrated, and at least one reservoir which is selectably in communication with the microneedles. wherein at least one of the reservoirs contains the therapeutic. prophylactic or diagnostic agent to be delivered; and

(b) a triggering device which is adapted to activate delivery of the agent from reservoir through the microneedles of one of the devices at a time.

41. A device for collecting a sample of a biological fluid comprising:

(a) one or more hollow or porous microneedles having a base end and a tip,

(b) a substrate to which the base of the microneedle is attached or integrated. and

(c) at least one collection chamber which is selectably in fluid communication with the base end of the microneedle.

42. The device of claim 41 further comprising

(d) a means for inducing transport of the biological fluid or component thereof into the collection chamber.

43. The device of claim 42 wherein the pressure within the collection chamber can selectively be reduced.

44. The device of claim 43 wherein the pressure reduction is induced by expanding the internal volume of the collection chamber.

45. The device of claim 44 wherein the collection chamber is a standard or Luer-lock syringe.

46. The device of claim 43 wherein the collection chamber comprises an upper portion which is formed of a material which is deformable.

47. The device of claim 43 further comprising a plunger movably secured to the substrate. wherein the plunger can deform the collection chamber.

48. The device of claim 46 further comprising a one-way valve.

49. The device of claim 41 wherein the collection chamber comprises a plurality of compartments.

50. The device of claim 41 comprising a three dimensional array of microneedles.

51. The device of claim 41 further comprising an adhesive material for securing the device to the biological barrier surface during fluid withdrawal or sensing.

52. The device of claim 41 further comprising a means for controlling flow through the microneedle.

53. The device of claim 42 wherein the means for controlling flow is a fracturable or removable barrier which is interposed between the collection chamber and base of the microneedle.

54. The device of claim 41 further comprising a sensor in communication with the collection chamber.

55. A device for sensing an analyte in a biological fluid, the device comprising:

(a) one or more microneedles having a base end and a tip,

(b) a substrate to which the base of the microneedle is attached or integrated.

(c) at least one sensor which is selectably in communication with the microneedle.

56. The device of claim 55 wherein the sensor comprises

a chemical or biochemical agent that react with the analyte, and

electrochemical or optical transducers which measure the reaction of the agent and analyte.

57. The device of claim 56 wherein the agent is an enzyme selected from the group consisting of glucose oxidase, glucose dehydrogensase, and combinations thereof.

58. The device of claim 55 further comprising an electronics package in communication with the sensor.

59. The device of claim 55 for insertion of the microneedles in skin and sensing of glucose.

60. A device for sensing an analyte in a biological fluid, the device comprising:

(a) one or more microneedles having a base end and a tip,

(b) a substrate to which the base of the microneedle is attached or integrated.

wherein at least one of the microneedles is or comprises a sensor.

61. The device of claim 60 wherein the sensor comprises

a chemical or biochemical agent that react with the analyte, and

electrochemical or optical transducers which measure the reaction of the agent and analyte.

62. The device of claim 60 further comprising an electronics package in communication with the sensor.

63. The device of claim 60 for insertion of the microneedles in skin and sensing of glucose.

64. The device of claim 41 wherein the collection chamber is adapted to receive and use glucose strips.

65. The device of claim 41 wherein the microneedle is hollow and comprises at least one opening in the side of the microneedle.

66. The device of claim 41 wherein the microneedle has a hollow bore containing a material to modulate the flow of biological fluid through the microneedles into the collection chamber.

67. A method for collecting a sample of a biological fluid or analyte therein, comprising the steps:

providing a device comprising (i) one or more hollow or porous microneedles having a base end and a tip, (ii) a substrate to which the base of the microneedle is attached or integrated, (iii) at least one collection chamber which is selectably in fluid connection with the base end of the microneedle, and (iv) a means for inducing transport of the biological fluid or component thereof into the collection chamber;

inserting the microneedles into a biological barrier comprising biological fluid; and

triggering the induction means to permit the transport of the biological fluid or a component thereof through the microneedles and into the collection chamber.

68. The method of claim 67 wherein the induction means is selected from capillary action, diffusion, mechanical pumps, electroosmosis, electrophoresis, convection, and combinations thereof.

69. The method of claim 67 wherein the induction means utilizes a pressure gradient in which the pressure within the microneedles and/or collection chamber is less than the pressure of the biological fluid adjacent the tip of the microneedle.

70. The method of claim 67 wherein the analyte to be collected or sensed is selected from the group consisting of glucose, cholesterol, bilirubin, creatine, metabolic enzymes, hemoglobin, heparin, clotting factors, uric acid, tumor antigens, reproductive hormones, oxygen, pH, alcohol, tobacco metabolites, and illegal drugs.

71. A method sensing an analyte in a biological fluid, comprising the steps:

(a) providing a device comprising (i) one or more hollow or porous microneedles having a base end and a tip, (ii) a substrate to which the base of the microneedle is attached or integrated, and (iii) at least one sensor which is in communication with one or more of the microneedles;

(b) inserting the microneedles into a biological barrier comprising biological fluid: and

(c) contacting the sensor with the biological fluid.

72. The method of claim 71 wherein the device further comprises (iv) at least one collection chamber which is selectably in fluid connection with the base end of the microneedle, and (v) a means for inducing transport of the biological fluid or component thereof into the collection chamber, and

wherein, after step (b), the induction means is triggered to draw the biological fluid or a component thereof through the microneedles and into the collection chamber.

73. The method of claim 72 wherein the induction means utilizes a pressure gradient in which the pressure within the microneedles and/or collection chamber is less than the pressure of the biological fluid adjacent the tip of the microneedle.

74. The method of claim 73 wherein the pressure gradient is created by increasing the volume within the collection chamber.

75. The method of claim 71 wherein the analyte to be collected or sensed is selected from the group consisting of glucose, cholesterol, bilirubin, creatine, metabolic enzymes, hemoglobin, heparin, clotting factors, uric acid, tumor antigens, reproductive hormones, oxygen, pH, alcohol, tobacco metabolites, and illegal drugs.

76. The method of claim 27 or 31 for sensing glucose wherein the biological barrier is human skin.

77. A device for transport of material or energy across or into an elastic biological barrier comprising

a microneedle having a tip end and a base end,

a substrate connected to the base end of the microneedle, and

a means for improving penetration of the biological barrier by the microneedle.

78. The device of claim 77 wherein the biological barrier is human or other mammalian skin.

79. The device of claim 77 wherein the means comprises one or more extensions (i) interposed between the substrate and the base end of the microneedle or (ii) extending from the side of the substrate distal to the base end of the microneedle.

80. The device of claim 79 wherein the extension is between about 500 μm and about 10 mm in height.

81. The device of claim 79 wherein the extension has a cross-sectional dimension of at least about 200 μm.

82. The device of claim 79 wherein the extension includes an array of microneedles extending therefrom.

83. The device of claim 79 wherein the extension is composed of a material which is different from the material forming the microneedles.

84. The device of claim 79 wherein the microneedle is hollow and wherein the extension includes at least one aperture in communication with the bore of the microneedle.

85. The device of claim 79 further comprising a rigid surface positioned apart from an array of the microneedles and oriented to contact an elastic biological barrier substantially at the same time as the microneedles when the microneedles are applied to the barrier.

86. The device of claim 77 wherein the substrate is curved.

87. The device of claim 77 comprising a plurality of microneedles of varying lengths.

88. The device of claim 87 comprising

four or more microneedles wherein the tip ends of the microneedles collectively define a curvilinear surface.

89. The device of claim 77 comprising a plurality of hollow microneedles in a linear array, wherein the substrate is mounted on a holder having one or more apertures through the holder in communication with the microneedles.

90. The device of claim 77 wherein the substrate is flexible.

91. The device of claim 90 wherein the substrate is deformable by fluid pressure or mechanical means.

92. The device of claim 91 wherein the substrate is mounted onto a flexible membrane bubble.

93. The device of claim 92 further comprising a second membrane bubble positioned to define a chamber between the flexible membrane bubble and the second membrane bubble.

94. The device of claim 93 wherein the chamber contains molecules which flow through the microneedle.

95. The device of claim 94 wherein the molecules are drug molecules.

96. The device of claim 77 wherein the means reduces the elasticity of the biological barrier.

97. The device of claim 96 wherein the means physically manipulates the biological barrier to present a more rigid surface in the area of the biological barrier to be penetrated by the microneedle.

98. The device of claim 97 wherein the manipulation is selected from the group consisting of stretching, pulling, pinching, and a combination thereof.

99. The device of claim 98 wherein the manipulation includes pulling by reducing the atmospheric pressure over the area of the biological barrier to be penetrated by the microneedles.

100. The device of claim 99 further comprising a body portion defining a first vacuum region and a second vacuum region.

wherein an array of microneedles separates the first and second regions.

101. The device of claim 100 wherein the body portion comprises an annular ring which holds the microneedles.

102. The device of claim 101 wherein the microneedle is hollow and wherein the body portion further comprises a means for attachment to a syringe, a conduit for connection to a vacuum pump, or both.

103. The device of claim 98 wherein the means for physically manipulating comprises a stretching cone or expandable ring around the microneedles.

104. The device of claim 98 wherein the means comprises a body portion from which a plurality of stretching elements are pivotally attached.

105. The device of claim 104 wherein the stretching elements have ends provided with a non-slip feature for engagement with the biological barrier.

106. The device of claim 98 wherein the means comprises jaws for pinching

a portion of the biological barrier for contact with the microneedles.

107. The device of claim 97 wherein the means comprises an adhesive film applied over the area of the biological barrier to be penetrated by the microneedle.

108. The device of claim 79 wherein the means for improving penetration creates holes in the stratum corneum, wherein the microneedle can be inserted into the holes.

109. The device of claim 108 wherein the means for creating holes is selected from the group consisting of thermal ablation, high pressure fluid puncturing, cryoablation, and application of degradation agents.

110. The device of claim 77 wherein the means for improving penetration accelerates the tips of the microneedles into the biological barrier, accelerates the biological barrier into contact with the tips of the microneedles, or a combination thereof.

111. The device of claim 110 wherein the means for accelerating the tip of the microneedle comprises releasing a spring or gas under compression.

112. The device of claim 77 wherein a lubricating material is incorporated into or coated onto the microneedle.

113. The device of claim 77 further comprising a collar to limit the depth of microneedle penetration.

114. The device of claim 77 further comprising a means for attaching the device to the skin of a patient, wherein the means is not the microneedle.

115. The device of claim 114 wherein the means is an adhesive film.

116. The device of claim 114 wherein the means is an arm band.

117. The device of claim 77 wherein the microneedle is hollow and wherein the device further comprises a reservoir selectably in communication with the hollow microneedle.

118. The device of claim 77 wherein the means for enhancing penetration comprises an apparatus for vibrating the microneedle.

119. The device of claim 118 wherein the apparatus comprises a piezoelectric transducer or an electromechanical actuator.

120. A kit of parts for use in transport of material or energy across or into an elastic biological barrier, comprising

(i) a device comprising one or more microneedles having a tip end and a

base end, and a substrate connected to the base end of the microneedle, and

(ii) an adhesive film or barrier-tightening chemical, either of which can be applied over an area of the biological barrier to be penetrated by the microneedle.

121. A method for transport of material or energy across or into an elastic biological barrier comprising using the device of any of claims 77-119.

122. The device of any of claims 1-36 and 41-66 further comprising a means for improving penetration of the biological barrier by the microneedles.